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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Application Number	Divisional of 09/603,713
		Filing Date	April 30, 2001
		First Named Inventor	Gerald Koelsch
		Group Art Unit	1653
		Examiner Name	Amal Mohamed
Sheet 1 of 11	Attorney Docket Number	OMRF 182 DIV	

U.S. PATENT DOCUMENTS						
Examiner Initials*	Cite No. <sup>1</sup>	US Patent Document		Name of Patentee or Applicant of Cited Document	Date of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code <sup>2</sup> (if known)			
		5,200,339		Abraham	04-06-1993	
		5,733,768		Dixon et al.	03-31-1998	
		5,942,400		Anderson et al.	08-24-1999	
		5,978,740		Armistead	11-02-1999	
		5,986,054		St. George-Hyslop et al	11-16-1999	
		6,077,682		Inouye et al.	06-20-2000	
AM		*6,207,710		Audia et al.	03-27-2001	Class / subclass C14 / 551

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Office. <sup>3</sup>	Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)				
		EP	0 855 444	A2	SmithKline Beecham Pharmaceuticals	07-29-1998		
		JP	10 108 681	A	SmithKline Beecham Corp	04-28-1998		
		WO	96/40885	A2	Athena Neurosciences, Inc.	12-19-1996		
		WO	97/27296	A1	HSC Research and Development Limited Partnership; The Governing Council of the University of Toronto	07-31-1997		
		WO	98/13488	A2	Schering Aktiengesellschaft	04-02-1998		
		WO	98/15828	A1	Scios, Inc.	04-16-1998		
		WO	98/21589	A1	The Trustees of the University of Pennsylvania	05-22-1998		
		WO	98/26059	A1	Athena Neurosciences, Inc.	05-18-1998		
		WO	99/51752	A1	Chugai Seiyaku Kabushiki Kaisha	10-14-1999		

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		WO	99/64587 A1		Rhon-Poulenc Rorer	12-16-1999		
		WO	00/17369 A3		Pharmacia & Upjohn Co.	03-30-2000		
		WO	00/23576 A3		Vivian Hook	04-27-2000		
		WO	00/47618 A2		Elan Pharmaceuticals, Inc.	08-17-2000		
		WO	00/58479 A1		Amgen, Inc.	10-05-2000		
		WO	00/77030 A1		Elan Pharmaceuticals, Inc.	12-21-2000		
		*WO	01/23533 A2		Pharmacia and Upjohn Co.	04-05-2001		

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OTHER ART -- NON PATENT LITERATURE DOCUMENTS			
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		<del>ABAD-ZAPATERO, et al., "Structure of a secreted aspartic protease from <i>C. albicans</i> complexed with a potent inhibitor: implications for the design of antifungal agents," <i>Protein Sci</i> 5(4):640-52 (1996).</del>	
		<del>ABBENATE, et al., "Inhibitors of -amyloid formation based on the -secretase cleavage site," <i>Biochemical and Biophysical Research Communications</i> 268(1):133-135 (2000).</del>	
		<del>ASKEW, et al., "Molecular recognition with convergent functional groups. Synthetic and structural studies with a model receptor for nucleic acid components," <i>J. Am. Chem. Soc.</i> 111, 1082-1090 (1989).</del>	
		<del>BAILEY &amp; COOPER, "A structural comparison of 21 inhibitor complexes of the aspartic proteinase from <i>Endothia parasitica</i>," <i>Protein Sci</i> 3(11):2129-43 (1994).</del>	
		<del>BRUNGER, et al., "Crystallography &amp; NMR system: A new software suite for macromolecular structure determination," <i>Acta Crystallogr D Biol Crystallogr</i> 54 ( Pt 5):905-21 (1998).</del>	
		<del>CAPELL, et al., "The proteolytic fragments of the Alzheimer's disease-associated presenilin-1 form heterodimers and occur as a 100-150-kDa molecular mass complex," <i>J Biol Chem</i> 273(6):3205-11 (1998).</del>	
		<del>CHARTIER-HARLIN, et al., "Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene," <i>Nature</i> 353(6347):844-6 (1991).</del>	
		<del>CITRON, et al., "Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production," <i>Nature</i> 360(6405):672-4 (1992).</del>	
		<del>COHEN, et al., "An artificial cell cycle inhibitor isolated from a combinatorial library," <i>Proc Natl Acad Sci USA</i> 95(24):14272-7 (1998).</del>	
		<del>CORDER, et al., "Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families," <i>Science</i> 261(5123):921-3 (1993).</del>	

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		<del>COWLEY, et al., "Alzheimer's unlocking the mystery," <i>Newsweek</i> January 31, 2000.</del>	
		<del>CUTFIELD, et al., "The crystal structure of a major secreted aspartic proteinase from <i>Candida albicans</i> in complexes with two inhibitors," <i>Structure</i> 3(11):1261-71 (1995)</del>	
		<del>DAVIES, "The structure and function of the aspartic proteinases," <i>Annu. Rev. Biophys. Chem.</i> 19:189-215 (1990).</del>	
		<del>DE STROOPER, et al., "Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein," <i>Nature</i> 391(6685):387-90 (1998).</del>	
		<del>DEALWIS, et al., "X-ray analysis at 2.0 Å resolution of mouse submaxillary renin complexed with a decapeptide inhibitor CH-66, based on the 4-16 fragment of rat angiotensinogen," <i>J. Mol. Biol.</i> 236(1):342-60 (1994).</del>	
		<del>DUNN, <i>Structure and Functions of the Aspartic Proteinases</i>, Adv. in Exptl. Med. Biol. 306 (Plenum Press, NY 1991).</del>	
		<del>ELLINGTON &amp; SZOSTAK, "In vitro selection of RNA molecules that bind specific ligands," <i>Nature</i> 346(6287):818-22 (1990).</del>	
		<del>ERMOLIEFF, et al., "Proteolytic activation of recombinant Pro-memapsin 2 (Pro-<math>\alpha</math>-secretase) studied with new fluorogenic substrates," <i>Biochemistry</i> 39(40):12450-12456 (2000)</del>	
		<del>FAN, et al., "BACE Maps to chromosome 11 and a BACE homolog, BACE2, reside in the obligate down syndrome region of chromosome 21," <i>Science</i> 286:1255a (1999)</del>	
		<del>FIELDS &amp; SONG, "A novel genetic system to detect protein-protein interactions," <i>Nature</i> 340(6230):245-6 (1989).</del>	

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		<del>KANG, et al., "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," Nature 325(6106):733-6 (1987).</del>	
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		<del>KELLY &amp; DOW, "Microbial differentiation: the role of cellular asymmetry," Microbiol Sci 1(9):214-9 (1984).</del>	
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		LEWIS & DEAN, "Automated site directed drug design: the concept of spacer skeletons for primary structure generation," <i>Proc R Soc Lond B Biol Sci</i> 236(1283):125-40 and 141-162 (1989).	
		LIN, et al., "Human aspartic protease memapsin 2 cleaves the -secretase site of -amyloid precursor protein," <i>PNAS</i> 97(4):1456-1460 (2000).	
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		MATSUMOTO, et al., "Molecular cloning of human cDNA with a sequence highly similar to that of the dihydrofolate reductase gene in brain libraries derived from Alzheimer's disease patients," <i>Eur. J. Biochem.</i> 230:337-343 (1995).	
		MCKINLAY & ROSSMANN, "Rational design of antiviral agents," <i>Annu Rev Pharmacol Toxicol</i> 29:111-22 (1989).	
		MECKELEIN, et al., "Identification of a novel serine protease-like molecule in human brain," <i>Molecular Brain Research</i> 66:181-197 (1998).	
		MULLAN, et al., "A locus for familial early-onset Alzheimer's disease on the long arm of chromosome 14, proximal to the alpha 1-antichymotrypsin gene," <i>Nat Genet</i> 2(4):340-2 (1992).	

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		<del>MULLAN, et al., "A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid," Nat Genet 4(5):345-7 (1992).</del>	
		<del>MURRELL, et al., "A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease," Science 254(5028):97-9 (1991).</del>	
		<del>NAVAZA, "AMoRe: an automated package for molecular replacement," Acta Crystallog Sect A 50:157 (1997).</del>	
		<del>OTWINOWSKI &amp; MINOR, "Processing of X-ray diffraction data collected in Oscillation mode," Methods Enzymol 276:307 (1997).</del>	
		<del>PEREZ, et al., "Enhanced release of amyloid beta protein from codon 670/671 "Swedish" mutant beta-amyloid precursor protein occurs in both secretory and endocytic pathways," J Biol Chem 271(15):9100-7 (1996).</del>	
		<del>PERRY &amp; DAVIES, QSAR: Quantitative Structure-Activity Relationships in Drug Design pp. 189-193 (Alan R. Liss, Inc. 1989).</del>	
		<del>PHIMISTER, "Four companies announce discovery of b-secretase gene," Nature Biotechnology 18:16 (2000).</del>	
		<del>PODLISNY, et al., "Presenilin proteins undergo heterogeneous endoproteolysis between Thr291 and Ala299 and occur as stable N- and C-terminal fragments in normal and Alzheimer brain tissue," Neurobiol Dis 3(4):325-37 (1997).</del>	
		<del>RIPKA, "Computers picture the perfect drug," New Scientist 54-57 (1988).</del>	
		<del>ROBAKIS, et al., "Molecular cloning and characterization of a cDNA encoding the cerebrovascular and the neuritic plaque amyloid peptides," Proc Natl Acad Sci U S A 84(12):4190-4 (1987).</del>	

Examiner's Signature	<i>Abdel A. Mohamed</i>	Date Considered	8/5/03
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Substitute for form 1449A/PTO  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Complete if Known	
		Application Number	Divisional of 09/603,713
		Filing Date	April 30, 2001
		First Named Inventor	Gerald Koelsch
		Group Art Unit	763
		Examiner Name	
Sheet 9 of 11	Attorney Docket Number	OMRF 182 DIV	

OTHER ART -- NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T <sup>2</sup>
		<del>ROBERTS &amp; SZOSTAK, "RNA-peptide fusions for the in vitro selection of peptides and proteins," Proc Natl Acad Sci U S A 94(23):12297-302 (1997).</del>	
		<del>ROGAEV, et al., "Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene," Nature 376(6543):775-8 (1996).</del>	
		<del>ROUVINEN, et al., "Computer aided drug design," Acta Pharmaceutica Fennica 97, 159-166 (1996).</del>	
		<del>RUMBLE, et al., "Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease," N Engl J Med 320(22):1446-52 (1989).</del>	
		<del>SEKOE, et al., "Translating cell biology into therapeutic advances in Alzheimer's disease," Nature 399(6738 Suppl):A23-31 (1999).</del>	
		<del>SHERRINGTON, et al., "Cloning of a gene bearing missense mutations in early onset familial Alzheimer's disease," Nature 375(6534):754-60 (1996).</del>	
		<del>SINHA &amp; LIEBERBURG, "Cellular mechanisms of beta-amyloid production and secretion," Proc Natl Acad Sci U S A 96(20):11049-53 (1999).</del>	
		<del>SINHA, et al., "Purification and cloning of amyloid precursor protein beta-secretase from human brain," Nature 402(6761):537-40 (1999).</del>	
		<del>STEINER, et al., "Expression of Alzheimer's disease-associated presenilin-1 is controlled by proteolytic degradation and complex formation," J Biol Chem 273(48):32322-31 (1998).</del>	
		<del>SUZUKI, et al., "An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants," Science 264(5163):1336-40 (1994).</del>	

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		Application Number	Divisional of 09/603,713		
		Filing Date	April 30, 2001		
		First Named Inventor	Gerald Koelsch		
		Group Art Unit	1653		
		Examiner Name			
Sheet	10	of	11	Attorney Docket Number	OMRF 182 DIV

OTHER ART -- NON PATENT LITERATURE DOCUMENTS			
Examiner's Initials <sup>1</sup>	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T <sup>2</sup>
		<del>SYMERSEY, et al., "High-resolution structure of the extracellular aspartic proteinase from Candida tropicalis yeast," Biochemistry 36(42):12700-10 (1997).</del>	
		<del>SZOSTAK, "In vitro genetics," TIBS 19:89, (1992).</del>	
		<del>TAGAWA, et al., "Alzheimer's disease amyloid -clipping enzyme (APP secretase): Identification, purification, and characterization of the enzyme," Biochemical and Biophysical Research Communications 177(1):377-387 (1991).</del>	
		<del>TAKAHASHI, Aspartic Proteases, Structure, Function, Biology, Biomedical Implications, Adv. in Exptl. Med. Biol. 362 (Plenum Press, NY 1995).</del>	
		<del>TANG, Acid Proteases, Structure, Function and Biology, Adv. In Exptl. Med. Biol. vol. 95 (Plenum Press, NY 1977).</del>	
		<del>TANG, et al., "Structural evidence for gene duplication in the evolution of the acid proteases," Nature 291(5646):618-21 (1979).</del>	
		<del>TANZI, et al., "Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease," Nature 331(6156):528-30 (1988).</del>	
		<del>The early story of Alzheimer's Disease, edited by Bick et al. (Raven Press, New York 1987).</del>	
		<del>THINAKARAN, et al., "Endoproteolysis of presenilin 1 and accumulation of processed derivatives in vivo," Neuron 17(1):181-90 (1996).</del>	
		<del>THINAKARAN, et al., "Evidence that levels of presenilins (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors," J Biol Chem 272(45):28415-22 (1997).</del>	

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		THIRAKARAN, et al., "Stable association of presenilin derivatives and absence of presenilin interactions with APP," <i>Neurobiol Dis</i> 4(6):438-53 (1998).	
		TURNER, et al., "Substrate specificity of memapsin 2 (-secretase): basis for inhibitor drug design for Alzheimer's disease," <i>Experimental Biology 2001 c/o FASEB Office of Scientific Meetings March 31-April 4, 2001, Orlando, Florida. (Abstract)</i>	
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		WOLFE, et al., "Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity," <i>Nature</i> 398(6727):513-7 (1999).	
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		YU, "Inhibition of beta-amyloid cytotoxicity by midkine," <i>Neurosci Lett</i> 254(3):125-8 (1998).	

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PTO-1449 REPRODUCED		ATTORNEY DOCKET NO. 2932.1008-003 (Formerly OMRP 182 DIV)		APPLICATION NO. 09/845,226	
<b>SUPPLEMENTAL INFORMATION DISCLOSURE CITATION IN AN APPLICATION</b> <b>February 3, 2003</b> (Use several sheets if necessary)		APPLICANT Gerald Koelsch, et al.			
		FILING DATE April 30, 2001		CONFIRMATION NO. GROUP 4183 11	
U.S. PATENT DOCUMENTS					
EXAM- INER INI- TIAL		DOCUMENT NUMBER	ISSUE DATE / PUBLICATION DATE		NAME
AM	AA	4,923,967	8 MAY 90		Bobbitt, et al. 350/35
	AB	5,221,607	22 JUNE 93		Cordell et al. 350/399
	AC	5,252,463	12 OCT 93		Nelson et al. 435/251
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AM	AK	6,329,163 B1	11 DEC 2001		Anderson, et al. 435/23
FOREIGN PATENT DOCUMENTS					
		DOCUMENT NUMBER	DATE	COUNTRY	CLASS SUB-CLASS TRANSLATION YES NO
AM	AL	WO 02/25276 A1	28 Mar 02	PCT	
AM	AM	WO 01/70672 A2	27 Sept 01	PCT	
AM	AN	0 302 469 A2	8 Feb 89	EPO	
	AO	WO 02/47466 A2	20-JUN-02	PCT	
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AM	AR	Ezzell, C., "Alzheimer's Alchemy," Science News 141:152-153 (1992).			
	AS	Majer, P., et al., "Structure-based subsite specificity mapping of human cathepsin D using statine-based inhibitors," Protein Science 6(7): 1458-1466 (1997).			
	AT	Martson, F.A.O. and Hartley, D., "Solubilization of protein aggregates," Methods in Enzymology 182: 264-276 (1990).			
AM	AU	Oefner, C., et al., "Renin inhibition by substituted piperidines: A novel paradigm for the inhibition of monomeric aspartic proteinases?" Chemistry & Biology (London) 6(3): 127-131 (1999).			
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Hadel A. Mohammed		8/5/03			

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 416681653

GROUP 1653

## U.S. PATENT DOCUMENTS

EXAM- INER INI- TIAL	DOCUMENT NUMBER	ISSUE DATE / PUBLICATION DATE	NAME
<del>AA3</del>	<del>6,420,534 B1</del>	<del>16 JUL 2002</del>	<del>Gurney et al.</del>
<del>AA2</del>	<del>US 2002/0081634 A1</del>	<del>27 JUN 2002</del>	<del>Gurney, et al.</del>
<del>AC2</del>	<del>US 2002/0055459 A1</del>	<del>09 MAY 2002</del>	<del>Chopra, et al.</del>
<del>AD2</del>	<del>US 2002/0072050 A1</del>	<del>13 JUNE 2002</del>	<del>Hook</del>
<del>AE2</del>	<del>US 2002/0037315 A1</del>	<del>28 MAR 2002</del>	<del>Gurney et al.</del>
<del>AF2</del>	<del>US 2002/0159991 A1</del>	<del>31 OCT 2002</del>	<del>Cordell, et al.</del>
<del>AG3</del>	<del>US 2002/0157122 A1</del>	<del>24 OCT 2002</del>	<del>Wong, et al.</del>
<del>AH2</del>	<del>US 2002/0111365 A1</del>	<del>15 AUG 2002</del>	<del>Wolfe, et al.</del>

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	AY	Turner, R.T., et al., "Subsite Specificity of Memapsin 2 ( $\beta$ -Secretase): Implications for Inhibitor Design," <i>Biochem.</i> 40(34):10001-6 (2001).
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	AS2	Howlett, D.R., et al., "In Search of an Enzyme: the $\beta$ -secretase of Alzheimer's disease is an aspartic proteinase," <i>Trends in Neurosci.</i> 23(11): 565-570 (2000).
	AT2	Ghosh, A.K., et al., "Structure-Based Design: Potent Inhibitors of Human Brain Memapsin 2 ( $\beta$ -Secretase)," <i>J. Med. Chem.</i> , 44:2865-2868 (2001).

EXAMINER

Abdel A. Mohammed

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